REMARKS/ARGUMENTS

Claims 29 and 31 have been canceled. Claims 19-28, 30 and 32-44 are active in the case. Reconsideration is respectfully requested.

The present invention relates to a process of preparing an aqueous suspension of drug particles to be administered to a subject by inhalation.

Claim Amendments

Claim 19 has been amended so that the claim expressly clarifies that in operation of the apparatus on an industrial scale, a vacuum is first applied to the turboemulsifier, and thereafter, the sterile micronized active ingredient is loaded into the solution in the turboemulsifier, where stirring and homogenization of the micronized active ingredient occurs. Support for these limitations can be found on pages 5 and 6 of the specification, as well as at page 6, lines 4-9. The median volumetric diameter of particles limitation recited in Claim 19 is supported by the disclosure at page 9, lines 19-21. Thus, the amendments do not introduce new matter into the case, and entry of the amendments is respectfully requested.

Claim Rejection, 35 USC 112

The amendment that has been made to Claim 42 is believed to be sufficient to overcome the issue that has been raised on non-reference grounds. Withdrawal of the rejection is respectfully requested.

Prior Art Rejection, 35 USC 102

Claims 9-44 stand rejected based on 35 USC 102 as anticipated by Bernini et al, WO 00/25746. This ground of rejection is respectfully traversed.

Before discussing features of the process described in '746, Applicants point out that the technical problem confronting them was to provide a process for the preparation of aqueous suspensions for nebulization which comprise a sterile micronized active ingredient. The process had to be applicable on an industrial scale, and would have to give rise to suspensions having an optimum, homogeneous and reproducible particle size distribution. All of these factors are essential for the production of formulations that have a high level of physical stability and therapeutic efficacy. Applicants have found that when the process of '746 is adapted to use in industrial scale operations by loading a micronized active ingredient from the top of a turboemulsifier at atmospheric pressure, a long processing time is required in order to disperse the active ingredient in a sterile solution. Further, the suspension which was obtained did not meet the requirement of homogeneity in a satisfactory manner. However, Applicants' have discovered that if the loading of the sterile active ingredient into the turboemulsifier is conducted through the turbine after a vacuum has been applied rather than from the top of the device at atmospheric pressure, it is possible to achieve a far more efficient dispersal of active ingredient, and therefore it is possible to prepare homogeneous suspensions with a distribution profile that is reproducible from one batch to the other, in a much shorter time. Moreover, because the micronized active ingredient is passed through the turbine under vacuum, it is possible to obtain finer particles, inside the emulsifier, that have a narrower, more homogenous particle size distribution range with no further need for additional treatments such as the high pressure homogenizer described in '746.

Turning now to the matter of anticipation, Applicants direct attention to Example 2 of the '746 document which discloses a preparation of an aqueous suspension formulation on a pilot plant scale of 100 litres. In this example the active ingredient is added to the sterile aqueous solution and is dispersed, initially by magnetic agitation only and then by using a turbine system for 15-20 minutes. The example does not contain any disclosure of how the

micronized active ingredient is loaded into the aqueous solution, and therefore does not show or suggest steps a) and b) of the present process.

Example 3 demonstrates a further distinction between the present process as claimed and the technique described in Example 2 of the patent. Example 3 of the patent shows the particle size distribution of particle samples of Example 2 that were stored under the conditions noted. In every instance, the median volumetric diameter of 90 % of suspended particles is always greater than 8 microns. (The particle size distribution data in Table 1 are of the active ingredient before the particles are suspended in solution.) Moreover, as stated on page 4 of the present specification, using the technique of Example 2 of the reference on the industrial scale may yield dispersions that do not meet the requirement of homogeneity in a satisfactory manner. The drawbacks of the procedure are largely attributable to the technological characteristics of the sterile micronized active ingredients which disperses more slowly, as well as more difficultly, in the aqueous vehicle than the unsterilized compound.

In view of the discussion above, it is clear that the '746 reference does not disclose a process which is suitable for industrial scale operations of volumes of material greater than 100 litres in giving rise to particle suspensions that have a narrow, homogeneous and reproducible particle size distribution. Moreover, the reference is completely silent about a particle size distribution wherein 90 % of the suspended particles of the active ingredients are of a size less than 8 microns.

Another difference between the method of the Bernini et al patent application and that of the invention is that the reference in several places, particularly on page 3, lines 10-11, discloses that the process optionally may be conducted under a vacuum in order to skim-off the aqueous suspension in the emulsifier. However, a "skimming-off of a suspension" is not what happens in the present process when a vacuum is applied to the turboemulsifier in the process of the present invention. Rather, the applied vacuum is necessary in order to realize a

reduction in particle diameter of the biologically active agent. This, in fact, is clearly demonstrated in the evidence provided in Table 2 of the specification which provides a contrast between Example 2 of the present invention and Preparation 2 of the '746 reference. The example of the reference does not employ the application of a vacuum to the turboemulsifier, so that micronization of the drug or pharmaceutical material does not occur by the application of a vacuum, but rather by the action of the emulsifier and the action of surfactants. The data in Table 2 on page 14 of the text clearly demonstrate the superior Feret diameter and median volumetric diameters with and without sonication of the aqueous drug containing medium that is prepared by the method of the invention (Prep 1) in contrast to the method of the reference (Prep 2). In fact, the method of the present invention is very effective in preparing a micronized active ingredient in a sterilized aqueous medium which possesses a high level of physical stability and therapeutic efficacy. Accordingly, given the remarks above, it is believed that the claimed process of the present invention which requires the application of a vacuum to the drug containing medium within a turboemulsifier is distinguished over the process disclosed in the reference in which the application of a vacuum is optional and employed for an entirely different purpose. Withdrawal of the anticipatory ground of rejection is respectfully requested.

Double Patenting

Claims 9-44 stand rejected based on the ground of non-statutory obviousness-type double patenting over Claims 2-9 and 13 of U.S. Patent 6,464,958. This ground of rejection is respectfully traversed.

As Applicants have stated above, an important aspect of the present process as claimed is the application of a vacuum to the aqueous drug containing in a turboemulsifier, because of the enhancement of the micronization of the active drug in the medium. On the

other hand, the claims of the '958 reference, although claiming a method of preparing an aerosol inhalable suspension of particles in a turboemulsifier, does not suggest a modification of the method in which a vacuum is applied to the emulsifier device. As seen from the discussion above, an applied vacuum is essential to achieving the micronization of a suspended drug in an aqueous medium in the present invention. Such a method is nowhere shown or suggested in '958. Accordingly, withdrawal of the rejection is respectfully requested.

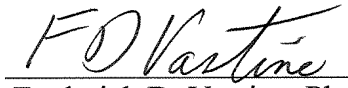
Claims 9-42 stand provisionally rejected based on the ground of non-statutory obviousness-type double patenting over Claims 1-20 of U.S. Patent Publication 2007/0140980. This ground of rejection is respectfully traversed.

The claimed process of the publication is the preparation of a sterile formulation in the form of an aqueous suspension for pulmonary administration by inhalation. The process is accomplished by the preparation of a sterile drug or active agent containing solution by filtration and separately a sterile aqueous phase containing excipients in a turboemulsifier followed by mixture of the two mediums and removal of the organic solvent to form the sterilized aqueous drug product. There is absolutely no suggestion in the claims of the use of a turboemulsifier alone that contains an aqueous drug or active agent containing medium, whereby the application of a vacuum is essential to achieve a desired micronization of the drug or active agent. Accordingly, the present invention as claimed is not obvious in view of the claims of the publication and withdrawal of the rejection is respectfully requested.

It is believed that the application is in proper condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Frederick D. Vastine, Ph.D.
Registration No. 27,013

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 06/04)